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Original Article

Factors Associated with Remission and/or Regression of Microalbuminuria in Type 2 Diabetes Mellitus

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The aim of this study was to clarify the factors associated with the remission and/or regression of microalbuminuria in Japanese patients with type 2 diabetes mellitus. We retrospectively analyzed the data of 130 patients with type 2 diabetes mellitus with microalbuminuria for 2–6 years (3.39 ± 1.31 years). Remission was defined as improving from microalbuminuria to normoalbuminuria using the albumin/creatinine ratio (ACR), and regression of microalbuminuria was defined as a decrease in ACR of 50% or more from baseline. Progression of microalbuminuria was defined as progressing from microalbuminuria to overt proteinuria during the follow-up period. Among 130 patients with type 2 diabetes mellitus with microalbuminuria, 57 and 13 patients were defined as having remission and regression, respectively, while 26 patients progressed to overt proteinuria. Sex (female), higher HDL cholesterol and lower HbA1c were determinant factors associated with remission/regression of microalbuminuria by logistic regression analysis. Lower systolic blood pressure (SBP) was also correlated with remission/regression, but not at a significant level. These results suggest that proper control of blood glucose, BP and lipid profiles may be associated with remission and/or regression of type 2 diabetes mellitus with microalbuminuria in clinical practice.

Key words: microalbuminuria, type 2 diabetes mellitus, remission, regression

The number of diabetes mellitus patients is dramatically increasing in Japan and has become public health challenge. It is well known that diabetic nephropathy is one of the most serious complications of diabetes mellitus. More than 300,000 patients in Japan undergo hemodialysis, and about 44% of those just starting hemodialysis in 2012 were affected by diabetes mellitus [1]. In addition, diabetic nephropathy is an independent risk factor for cardiovascular disease, and has a serious impact on quality of life and health care costs [2–7]. The earliest known manifestation of diabetic nephropathy is the presence of small amounts of albumin in the urine, called microalbuminuria [8]. In our country, more than 40% of patients with type 2 diabetes mellitus have microalbuminuria [9]. Recommended treatment of diabetic nephropathy is as follows: 1) tight control of blood

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glucose, 2) tight control of blood pressure (BP), 3) suppression of the renin-angiotensin system (RAS) using angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), 4) control of lipid profiles, 5) diet therapy, and 6) lifestyle modification (including smoking cessation) [9]. In patients with type 2 diabetes mellitus, the course of renal dysfunction is more heterogeneous, and the natural progression less well characterized than in patients with type 1 diabetic nephropathy [10]. Furthermore, for a wide variety of treatment methods, the impact of each treatment on preventing and improving diabetic nephropathy in patients with type 2 diabetes mellitus has not been fully examined in clinical practice.

In the present study, we evaluated the remission/regression vs. progression of microalbuminuria in Japanese patients with type 2 diabetes mellitus in a single clinical practice. In addition, we clarified the factors that are associated with remission and/or regression of microalbuminuria.

Subjects and Methods

Subjects. We retrospectively collected the data of 130 subjects who met the following criteria: (1) diagnosed as having type 2 diabetes mellitus in accordance with the criteria of the Japanese Diabetes Society [11] and the World Health Organization [12] at the Department of Medicine, Okayama University Hospital between January 2006 and December 2009; (2) having microalbuminuria by at least 2 measurements of albumin/creatinine ratio (ACR) in a spot urine sample, and their diabetic nephropathy status was determined; (3) having no complicating cancer, liver disease, collagen disease, or nondiabetic kidney disease confirmed by renal biopsy; and (4) having received follow-up physical examinations at least every two months, while undergoing measurements of ACR in a spot urine sample at least once a year for 2–6 years.

All participants received treatment based on the standard strategies for diabetes mellitus, hypertension, and dyslipidemia during these periods.

This study was approved by the Ethics Committee on Epidemiological Studies of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences.

Assessment of urinary albumin excretion. The albumin excretion rate was estimated on the basis of the ACR in spot urine samples, as previously described [13–15]. The levels of albumin excreted in each measurement of ACR were classified as normoalbuminuria (ACR < 30 mg/g creatinine), microalbuminuria ($30 \leq$ ACR < 300 mg/g creatinine), and overt proteinuria (ACR ≥ 300 mg/g creatinine).

Criteria for remission, regression and progression of microalbuminuria. We applied the criteria of previous reports for remission, regression and progression of microalbuminuria [16, 17]. Remission of microalbuminuria was defined as returning to normoalbuminuria during the follow-up period; regression of microalbuminuria was defined as a decrease in ACR of 50% or more from baseline. Otherwise, progression of microalbuminuria was defined as progressing from microalbuminuria to overt proteinuria during the follow-up period.

Clinical parameters. All data were retrospectively obtained from electronic charts. Body mass index (BMI) was the weight in kilograms divided by the square of the height in meters. The estimated Glomerular Filtration Rate (eGFR) was calculated using the following equation: eGFR (ml/min/1.73 m^2) $= 194 \times \mathrm{Cr}^{-1.094} \times \mathrm{Age}^{-0.287} \times 0.739$ (a constant derived specifically for women) [18]. Among antihypertensive drugs, RAS blockade drugs including ACE inhibitors or ARBs and other antihypertensive drugs were separately recorded and analyzed.

Statistical analysis. Values are expressed as means ± standard deviations (SDs) for continuous variables. The participants were classified by the course of microalbuminuria, remission and/or regression, no change and progression. One-way analysis of variance (ANOVA) and Tukey's F test were used to compare among 3 groups. Participants were also classified as being with or without remission/regression of microalbuminuria during the follow-up period. Comparisons between these 2 groups was performed using Chi-squared tests for categorical variables and unpaired t tests for continuous variables. Univariate and multivariate analyses were also performed using a logistic regression model.

To investigate the importance of each clinical practice recommendation, we dichotomized the levels of HbA1c, BP, and lipid profiles as salutary or nonsalutary. The salutary levels were defined as follows: HbA1c < 6.5%, BP $< 130/80$ mmHg, and lipid profiles

<150 mg/dl for triglycerides, <120 mg/dl for LDL cholesterol, and ≥ 40 mg/dl for HDL cholesterol, according to the clinical practice recommendations of the Japanese Diabetes Society [19]. We then coded each follow-up period of observation on a scale from 0 to 3 according to the number of the 3 factors with a salutary level, and calculated hazard ratios.

All statistical analyses were performed using the SPSS 21.0 software program for Windows. We selected p values <0.05 as the threshold of statistical significance in all tests.

Results

During the follow-up period (average of 3.4 years), among 130 type-2 diabetes mellitus patients with microalbuminuria, 57 patients (43.8%) demonstrated remission of microalbuminuria, 13 patients (10.0%) demonstrated regression of microalbuminuria, and 26 patients (20.0%) progressed to overt proteinuria. The remission/regression rate was higher than that of progression.

The clinical characteristics of the patients at baseline according to the course of microalbuminuria are summarized in Table 1. Among participants with remission and/or regression of microalbuminuria, the proportions of males and alcohol drinkers were significantly lower than those in other categories. In participants with progression of microalbuminuria, systolic BP, ACR and diabetic retinopathy were significantly higher than those in other participants. In participants with remission/regression of microalbuminuria, HDL cholesterol was significantly higher than that in participants with progression of microalbuminuria.

Next, we compared the clinical characteristics

Table 1 Clinical characteristics of the study participants at baseline according to the course of microalbuminuria

	Remission and/or Regression	No change	Progression
Number of participants: n (%)	70 (53.8)	34 (26.2)	26 (20.0)
Male sex: n (%)	30 (42.9)[ab]	24 (70.6)	20 (76.9)
Age (years)	59.9 ± 14.3	62.0 ± 13.8	64.3 ± 11.5
Duration of diabetes (years)	9.6 ± 7.9	10.7 ± 10.1	14.2 ± 11.2
Current smoking: n (%)	16 (27.6)	8 (27.6)	12 (50.5)
Alcohol drinker: n (%)	12 (20.7)[ab]	15 (50.0)	11 (45.8)
Body mass index (kg/m^2)	25.3 ± 4.5	25.7 ± 4.7	24.6 ± 4.1
Systolic blood pressure (mmHg)	128.9 ± 14.7[b]	132.1 ± 11.4[b]	141.2 ± 15.9
Diastolic blood pressure (mmHg)	74.7 ± 9.5	74.9 ± 11.6	79.0 ± 12.4
HbA1c (%)	7.5 ± 1.4	7.4 ± 1.0	7.7 ± 1.5
Plasma glucose (mg/dl)	168.0 ± 58.1	181.5 ± 60.2	178.2 ± 49.6
BUN (mg/dl)	17.2 ± 8.5	17.2 ± 6.6	18.3 ± 4.9
Serum creatinine (mg/dl)	0.81 ± 0.73	0.86 ± 0.25	0.88 ± 0.32
Estimated Glomerular Filtration Rate (ml/min/1.73m^2)	79.6 ± 28.0	70.1 ± 20.3	71.8 ± 25.2
ACR (mg/g creatinine)	69.6 ± 61.6[b]	79.0 ± 73.9[b]	152.9 ± 107.2
Uric acid (mg/dl)	5.2 ± 2.0	5.6 ± 1.4	5.5 ± 1.4
Total cholesterol (mg/dl)	198.0 ± 34.1	204.7 ± 31.8	184.1 ± 38.9
Triglycerides (mg/dl)	147.4 ± 90.7	178.9 ± 113.7	158.9 ± 157.8
HDL cholesterol (mg/dl)	60.1 ± 15.9[b]	54.0 ± 16.1	50.4 ± 12.6
LDL cholesterol (mg/dl)	111.7 ± 28.6	117.3 ± 29.6	103.9 ± 24.9
Diabetic neuropathy: n (%)	26 (39.4)	13 (40.6)	15 (60.0)
Diabetic retinopathy: n (%)	23 (33.8)[b]	8 (25.8)[b]	16 (61.5)
IHD: n (%)	8 (11.4)	4 (11.8)	4 (15.4)
CVD: n (%)	3 (4.3)	2 (5.9)	2 (7.7)
PAD: n (%)	2 (2.9)	2 (5.9)	1 (3.8)
Use of ACE inhibitor or ARBs: n (%)	30 (42.9)	18 (52.9)	16 (61.5)
Use of Statin: n (%)	20 (28.6)	12 (35.5)	6 (23.1)

Data are means ± SD unless otherwise indicated. IHD, ischemic heart disease. CVD, cerebral vascular disorder. PAD, peripheral arterial disease.

[a]$p<0.05$ versus no change. [b]$p<0.05$ versus progression.

between patients with and without remission/regression in the follow-up period. In the univariate analysis, significant differences of plasma glucose, HbA1c, creatinine and BUN were noted between the 2 groups (Table 2). To adjust for confounding factors such as duration of diabetes, total cholesterol and smoking habits by logistic regression analysis, we found that the female sex [odds ratio (OR): 4.34, (95% confidence interval (CI): 1.70–11.12), $p = 0.002$], higher HDL cholesterol (≥ 50 mg/dl) [OR: 3.65, (95% CI: 1.06–9.88), $p = 0.031$] and lower HbA1c ($\leq 6.0\%$) [OR: 5.61, (95% CI: 1.13–27.85), $p = 0.035$] were independently associated with remission/regression of microalbuminuria (Table 3), whereas lower SBP (≤ 130 mmHg) [OR: 2.66, (95% CI: 0.83–7.23), $p = 0.122$] was weakly associated with remission/regression of microalbuminuria, *i.e.*, not at a significant level.

Table 2 Clinical characteristics of the study participants at follow-up according to the presence or absence of remission and/or regression of microalbuminuria

	Remission and/or Regression	No Remission and/or Regression	*p* value
Mean follow-up time (years)	2.8 ± 1.1	4.1 ± 1.6	<0.001*
Body mass index (kg/m^2)	25.4 ± 4.3	25.3 ± 4.4	0.893
Systolic blood pressure (mmHg)	129.3 ± 11.6	131.1 ± 12.0	0.398
Diastolic blood pressure (mmHg)	73.6 ± 9.1	73.6 ± 11.0	0.991
HbA1c (%)	6.7 ± 0.8	7.2 ± 1.2	0.023*
Plasma glucose (mg/dl)	151.1 ± 32.2	168.8 ± 52.4	0.028*
BUN (mg/dl)	16.3 ± 4.6	18.7 ± 6.4	0.020*
Serum creatinine (mg/dl)	0.75 ± 0.20	0.91 ± 0.29	<0.001*
Estimated Glomerular Filtration Rate (ml/min/1.73m^2)	71.4 ± 21.2	64.9 ± 19.7	0.079
Uric acid (mg/dl)	5.4 ± 1.3	5.7 ± 1.3	0.215
Total cholesterol (mg/dl)	190.5 ± 25.1	192.2 ± 43.3	0.793
Triglycerides (mg/dl)	134.9 ± 71.4	161.0 ± 117.9	0.131
HDL cholesterol (mg/dl)	55.6 ± 14.7	51.6 ± 12.8	0.117
LDL cholesterol (mg/dl)	109.5 ± 19.9	105.2 ± 22.1	0.254
Use of ACE inhibitor or ARBs: n (%)	39 (55.7)	41 (68.3)	0.153
Use of Statin: n (%)	24 (34.3)	31 (51.7)	0.074

Data are means ± SD unless otherwise indicated. *$p < 0.05$.

Table 3 The ORs of factors associated with the remisson and/or regression of microalbuminuria with the logistic regrsssion model

Factor	Adjusted odds ratio	95% confidence interval	*p* value
Sex (female)	4.34	1.70–11.12	0.002*
HDL cholesterol (mg/dl)			0.031*
HDL < 40	1	ref.	
40 ≤ HDL < 50	1.10	0.23–3.06	
50 ≤ HDL < 60	3.65	1.06–9.88	
60 ≤ HDL	4.17	1.20–11.53	
HbA1c (%)			0.035*
7.0 < HbA1c	1	ref.	
6.5 < HbA1c ≤ 7.0	3.53	0.67–18.63	
6.0 < HbA1c ≤ 6.5	4.26	0.83–21.92	
HbA1c ≤ 6.0	5.61	1.13–27.85	
Systolic blood pressure (mmHg)			0.122
140 < SBP	1	ref.	
130 < SBP ≤ 140	1.42	0.51–3.76	
SBP ≤ 130	2.66	0.83–7.23	

The multivariate model was adjusted for BMI, duration of diabetes, total cholesterol, smoking habits, and use of ACE inhibitor or ARBs. Ref., reference category. *$p < 0.05$.

Finally, the clinical importance of recommended guidelines for glycemic exposure, BP and lipid profiles was evaluated by the multivariate model adjusted for sex and use of ACE inhibitor or ARBs. The hazard ratio for the remission/regression of microalbuminuria increased with each increment in the number of factors at a salutary level (Fig. 1), when 3 factors, as compared with none, were at the salutary levels, the hazard ratio for remission/regression of microalbuminuria was 1.489 (95% CI: 0.625–3.550), but not at a significant level.

Discussion

Microalbuminuria in patients with type 2 diabetes mellitus has been considered the first step toward overt proteinuria and renal failure. However, our results indicate that microalbuminuria can improve to normal levels in some Japanese type 2 diabetes mellitus patients. Among 130 patients with microalbuminuria, only 20% of patients progressed to overt proteinuria, whereas 40% of patients improved to normoalbuminuria.

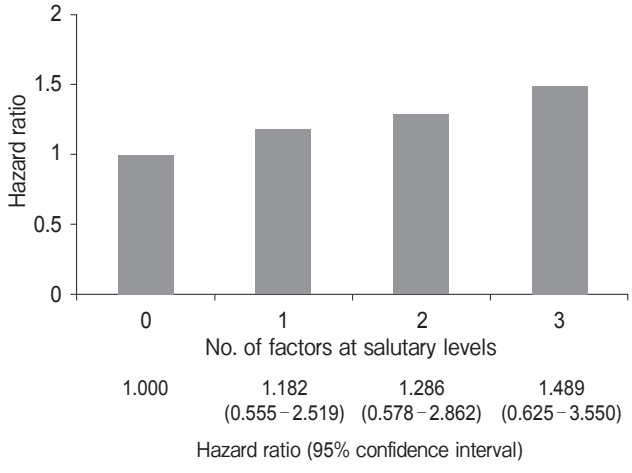

Fig. 1 Additive effects of factors at salutary levels on remission and/or regression of microalbuminuria. Salutary levels of the various factors were defined as < 6.5% for HbA1c, a combination of < 130 mmHg of systolic blood pressure and < 80 mmHg of diastolic blood pressure, and a combination of < 150 mg/dl of triglyceride, < 120 mg/dl of LDL cholesterol, and ≥ 40 mg/dl of HDL cholesterol. The reference category was considered to be the absence of a salutary level for any of the 3 factors. The estimates were adjusted for sex, and use of ACE inhibitor or ARBs. The number of patients having 0, 1, 2, and 3 factors at salutary levels were 23 (18.1%), 47 (37.0%), 40 (31.5%), and 17 (13.4%), respectively.

This study also provided evidence that rigorous control of glycemic exposure, HDL cholesterol and SBP, and female sex were independently associated with the remission and/or regression of microalbuminuria. Improvement of microalbuminuria has recently been reported in patients with type 1 and type 2 diabetes mellitus. Perkins *et al.* found frequent regression, with 58% (95% CI: 52–64) incidence at the 6-year follow-up in patients with type 1 diabetes mellitus [16]. Araki *et al.* also found frequent remission and/or regression, with ～50% incidence at the 6-year follow-up in patients with type 2 diabetes mellitus [17]. These observations strongly indicate that microalbuminuria frequently regresses, contrary to our expectations. In this study, we additionally identified the factors associated with the reduction of microalbuminuria in type 2 diabetes mellitus.

The level of blood glucose seems to be the strongest factor influencing the onset of microalbuminuria. This has been demonstrated in several observational studies [13, 14, 20–23] as well as in clinical trials [24–27]. In our study, the lower HbA1c (≤ 6.0%) was independently associated with remission/regression of microalbuminuria. This cutoff value is lower than the recommended therapeutic target (< 7.0%) for HbA1c [19, 28]. Additionally, the Steno type 2 randomized study [29] showed that the target HbA1c level to prevent progression of diabetic nephropathy was < 6.5%. In our study, the ORs for remission/regression of microalbuminuria in subjects with HbA1c < 7.0% was not statistically significant (OR: 3.68, 95% confidence interval: 0.71–17.33). Our participants' mean HbA1c at baseline (7.2 ± 1.0%) was lower than in other previous studies.

Essential hypertension [30–33], elevated SBP [23, 32], cigarette smoking [14, 34], elevated levels of serum cholesterol and triglycerides [22], and genetic susceptibility are risk factors for diabetic nephropathy [35]. Maintaining BP < 130/80 mmHg is recommended in diabetic patients for preservation of renal function and reduction of cardiovascular events [19, 28, 36]. In our study, lower SBP (≤ 130 mmHg) and lower DBP (≤ 80 mmHg) were not independently associated with remission/regression of microalbuminuria because our participants' mean SBP and DBP at baseline (130.6 ± 10.8 mmHg, 75.3 ± 8.5 mmHg) were comparably well controlled. In lipid profiles, HDL cholesterol was independently associated with

improvement of microalbuminuria. We thought that LDL cholesterol might not have been statistically significant in our study because LDL cholesterol was well controlled by the use of statins, especially in participants with progression of microalbuminuria. These results suggest that normalization of the lipid profile may be associated with remission/regression of type 2 diabetes mellitus with microalbuminuria.

Sex is one of the risk factors for microvascular complications, as well as blood glucose, BP, lipids and cigarette smoking. However, there have been few reports relating sex to the incidence/prevalence and the pathological condition of microvascular complications. There have been a few studies regarding sex as a risk factor for nephropathy, with different results. In a German study of type 1 diabetes mellitus patients, male sex was a risk factor for evident nephropathy [37]. In a study of UKPDS, male sex was a risk factor of an evident albumin urocrisis [38]. In the report of Takane *et al.*, the time when diabetes mellitus and nephropathy were diagnosed tended to be earlier in men than in women, and the dialysis induction age was significantly lower in men [39]. Daniels *et al.* showed that female sex associated with an increased frequency of microalbuminuria in children and adolescents with type 1 diabetes mellitus [40]. In this study, the rate of remission/regression of microalbuminuria was significantly higher in female patients. Future studies investigating sex-specific interventions to reduce the incidence and rate of progression of diabetic nephropathy are required.

Potential limitations still remain in our study. First, the definition of regression of microalbuminuria is not generally recognized. We defined regression of microalbuminuria as a decrease in ACR of $\geq 50\%$ from baseline, as in the Joslin Diabetes Center study and Shiga University study [16, 17]. This definition does not always reflect changes in renal function. It remains unclear whether a decrease in ACR of ≥ 50 percent reflects improvements in morphological abnormalities. Second, our study did not clarify whether remission and/or regression of microalbuminuria finally results in a reduction of the incidence of end-stage renal disease (ESRD) or cardiovascular mortality. Because the average observation period was short, continuation of the observation over the long term is necessary to confirm the results. Third, we examined biochemical measurements in spot blood samples, so blood glucose and triglycerides were not evaluated. Fourth, the small sample size made it difficult to prove the factors that are associated with remission/regression of microalbuminuria, or to investigate the importance of each clinical practice recommendation separately.

In conclusion, we revealed the conditions for improvement of microalbuminuria in patients with type 2 diabetes mellitus at a typical Japanese clinic. These results suggest that management of blood glucose and BP are beneficial and useful measures for the remission and/or regression of microalbuminuria. Lipid profiles, especially higher level of HDL cholesterol, might also be important for remission/regression of microalbuminuria. In addition, the possibility of sex-specific interventions to reduce the incidence and rate of progression of diabetic nephropathy was suggested.

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